REMARKS

Claim 24 is the only claim that remains in the application.

Applicants wish to express their appreciation for the courtesies extended to applicant's representative, Dr. Kenneth I. Kohn, during a personal interview on December 17, 2008. During the interview, Dr. Kohn gave an overview of the art of record and discussed proposed claim 24. There was an indication that evidence of unexpected results with specific regard to pending claim 24, would place the application in condition for allowance. Applicant respectfully directs attention to Example 2 which clearly shows unexpected results of the MIMP enhancement of T-cell immune response by subcutaneous immunization with a flu vaccine. The antibody data is presented in figure 9 of the application. Likewise, Example 3 shows unexpected results with a flu vaccine by intramuscular immunization. Example 4 provides unexpected results in response to influenza vaccination in aged mice, showing the unexpected significance with regard to the agent. Accordingly, the application as filed provides significant evidence of unexpected results commencing the scope with presently pending claim 24. Accordingly, applicant has provided herewith evidence of unexpected results as requested by the examiner during the aforementioned interview.

Claim 24 claim was rejected under 35 U.S.C. §103(a) as being unpatentable over the reference to Masihi in view of Baumgarth, et al. Specifically, the Office Action holds that Masihi teaches preparations containing thymus extracts are used for therapy of immune defects in infectious diseases. Combination therapy with thymosin-α1, interferon-α and AZT in patients was associated with a substantial increase in the number and function of CD4+ T cells. Thymosin-α1, interferon-α, and amantadine combination was shown to be effective for influenza virus infection. Masihi also teaches that MIMP has been shown to enhance mitogen-induced proliferation of lymphocytes, augment IgM plaque-forming cells, induce delayed type hypersensitivity and normalize an impaired response to IL-1. The Office Action holds that Masihi does not explicitly teach treating

influenza with MIMP; however one skilled in the art would have had a reasonable expectation of success in employing any compound functionally described as being thymomimetic for treating influenza. Masihi also does not explicitly teach detecting a T-cell response; however, it would have been obvious to one skilled in the art to monitor T-cell response in patients undergoind influenza treatment in view of Baumgarth, et al. The Office Action holds that Baumgarth, et al. teaches the importance of T-cells for recovery from influenza virus infection and teaches monitoring T-cell response in accessing the effectiveness of influenza treatment regimens. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over Masihi in view of Baumgarth, et al. is respectfully requested.

> "Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).
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> "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP Section 2143.
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> "The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." *KSR International Co. v. Teleflex Inc.*, 83 UDPQ2d 1385, 1395 (2007) and MPEP Section 2143.

It is undisputed that Masihi teaches that the immune system can be manipulated either specifically by vaccination or non-specifically by immuno-modulation as set forth on pages 181-182, as cited in the Office Action. This generally is the crux of the Masihi article. Masihi discloses that this is critical since the focus of the medical community prior to the Masihi publication was overtly focused on a targeting microbial pathogens and

ignoring strategies toward enhancing host immunity. Masihi recognized a problem due to increased drug resistance and multi-drug resistance leaving experts concerned about a post-antibiotic era. Accordingly, Masihi reviewed a "diverse array of natural, synthetic, and recombinant immuno-modulators" in his article, disclosing how each one specifically potentiated or stimulated host defense mechanisms.

More specifically, the Masihi disclosure discussed immuno-modulators as a general category, focusing on non-specific stimulation of the immune system. The Masihi review focused on "immuno-stimulatory non-antibiotic agents capable of enhancing host defense mechanisms" and "augmentation of the anti-infectious immunity by the cells of the immune system" (page 181, col. 2). On page 184 of the Masihi article, in the paragraph bridging columns 1 and 2, Masihi discusses methyl inosine monophosphate (MIMP) as "an interesting thymomimetic immuno-modulator capable of inducing the expression of T-lymphosite differentiation markers in human prothymocytes." Specifically, the Masihi article discloses that MIMP has been shown to enhance mytogen-induced proliferation of lymphocytes, augment IgM plaque-forming cells, induce delayed type hypersensitivity, and normalize an impaired mouse response to IL-2. With specific regard to MIMP, the Masihi patent does not disclose or suggest the specifically claimed limitations of independent claim 24; that being the administration of the protected IMP compound, detecting a T-cell response, and treating influenza. Applicant is well aware of Masihi's disclosure as Masihi for this section of his article is quoting one of the present inventor's article, published in 1992. Hence, Masihi is merely quoting the present inventors own article noting interesting cellular responses produced by MIMP, but not at all knowing or anticipating or even hypothesizing the presently claimed invention.

Furthermore, while Masihi mentions other compounds such as thymosin-α1 that produce a T-cell effect, there is no disclosure of a T-cell effect with MIMP therein. At the time of the present invention, it had been believed that MIMP provided only a B-cell response. This is described in the present invention in paragraph [0026], emphasis added.

[0026] Another experiment has also been performed to assess the utility of MIMP as an oral vaccine adjuvant (U.S. Pat. No. 5,614,504). Certain mice strains are poor responders to the hepatitis B surface antigen ("HbsAg") based vaccine (given as part of a Dane's particle type vaccine). Mice are given MIMP (50 mg/kg) orally 30 minutes prior to immunization or intraperitoneally simultaneously with immunization. One group also received oral MIMP for an additional 3 days after the simultaneous administration with immunization (MIMP daily group). Immunization is 16 mg of antigen per mouse in PBS at day 0 and 14. Antibody titer is assessed after primary immunization and booster immunization. ***While this study demonstrated an increase in antibody titer (B-cell response), it did not demonstrate that MIMP could enhance T-cell immune activity.***

Thus, while MIMP was included in the Masihi reference with many other immunomodulators, some of which provide a T-cell response, there is no reason why one skilled in the art would believe MIMP creates a T-cell response. Knowing that a T-cell response is one that is important for recovery from influenza virus infection based on Baumgarth, et al., one skilled in the art would not choose to administer MIMP to a patient because it had never been shown to provide a T-cell response prior to Applicant's experiments detailed in the examples. Baumgarth, et al. also does not disclose anything about MIMP, but merely that other immunomodulators do provide a T-cell response, basically confirming the information that is taught in Masihi, i.e. that *some* immunomodulators provide T-cell responses. Baumgarth, et al. in fact teaches away from the present invention because one would only administer a compound that is known to have a T-cell response to someone suffering from influenza. Based on knowledge about MIMP at the time of the present invention, one skilled in the art would have concluded that MIMP was not effective against influenza because it only provided a B-cell response. Furthermore, Masihi addresses issues of antibiotics and therefore is focused on bacterial infections and their growing tolerance to antibiotics. The presently pending claim is directed to influenza, which is virally induced. There is no nexus between the disclosure of Masihi and the mechanism of the present invention. Therefore, one skilled in the art would not look to Baumgarth, et al. to improve treatments disclosed in Masihi.

The presently pending method claim includes method steps that are not at all contemplated or disclosed in the reference, as the reference cites one of the present inventor's own article of which he is intimately aware and knowledgeable of. Again, at best, the Masihi article discloses that MIMP, specifically, is an interesting thymomimetic immunomodulator that induces various cellular responses, but absolutely, there is no disclosure that such a compound or a protected IMP compound in general, can successfully treat influenza, and that one can detect a T-cell response in such treatments. There is absolutely and undisputably no such disclosure in the Masihi reference. Such a discovery therefore must be considered invention over the prior art especially since such a discovery is such a tremendous clinical leap in medicine.

If the Masihi article in combination with Baumgarth, et al. is considered as a basis for a *prima facia* obviousness-type rejection which is rebuttable by factual evidence of unexpected results as a matter of law, then Applicant directs attention to the various examples set forth in the presently pending application which clearly demonstrate the unexpected results of the present invention as a treatment for, and as a prophylaxis for, influenza. Although all the examples in the application are relevant, specific attention is drawn to examples 3, 5 and 6 wherein immune response is clearly demonstrated in example 3 and pre-exposure protection is clearly shown to be conferred in examples 5 and 6. Amazingly, Figures 7 and 8, for the first time, show unequivocal enhancement of T-cell response to HIV vaccine. Hence, the present application provides factual evidence of examples of undeniably unexpected results as such results were previously not shown in any art and certainly were not disclosed in the Masihi article or any article quoted by Masihi, or in Baumgarth, et al. Hence, it is respectfully submitted, that as a matter of law, Applicants present factual evidence that would rebut a *prima facia* obviousness rejection if such was held based on the Masihi reference in combination with Baumgarth, et al.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to

be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

In view of the above, it is respectfully submitted that the presently pending independent claims be allowed.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

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I hereby certify that this correspondence is being electronically filed with the United States Patent & Trademark Office on the above date.

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